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Catalytic Hydrolysis of Phosphate Monoesters by Lanthanide(III) Cryptate (2.2.1) Complexes

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The hydrolysis of 4-nitrophenyl phosphate is catalysed by lanthanide(III) (2.2.1) complexes, and kinetic studies reveal that the europium(III) (2.2.1) chloride (c = 4.0 mmol dm^{-3}) hydrolyses the phosphate monoester at an enhanced rate (k_{p1} = 1.7 × 10^{-4} s^{-1} at pH 7.5 and 50 °C), with a turnover number of 4; the pH dependence of the rate constants is well correlated with the concentration of the lanthanide (2.2.1) hydroxides.

The hydrolysis of phosphate monoesters has attracted attention in relation to the hydrolysis of phosphate diesters, the backbone of DNA. Since the former is a primary product of the hydrolysis of the latter, the fate of phosphate monoester is a matter of considerable interest.[1] While large enhancement of rates has been achieved for the hydrolysis of phosphate monoesters with transition metal complexes,[2–5] only a few examples are catalytic.[3a] In many cases the phosphate monoesters bind to the metal centre so strongly that a desirable catalytic cycle for the hydrolysis is blocked.[6]

It is reasonable that lanthanide(III) ions should be most efficient metal centres in catalysing and promoting the hydrolysis of phosphate esters, since lanthanide(III) ions have high ionic potential (Z^2/r), high coordination numbers, and outstanding substitution lability.[7] Here we report our observation that the lanthanide(III) cryptate (2.2.1) complexes (1a, b)[8] are able to *catalyse* the hydrolysis of 4-nitrophenyl phosphate (NPP) at remarkable rates [eqn. (1)].

$$O=\overset{\overset{\displaystyle O^-}{|}}{\underset{\underset{\displaystyle O^-}{|}}{P}}-O-\!\!\!\left\langle\!\!\!\bigcirc\!\!\!\right\rangle\!\!\!-NO_2 \longrightarrow \begin{matrix}\text{inorganic}\\\text{phosphate}\\(P_i)\end{matrix} + HO-\!\!\!\left\langle\!\!\!\bigcirc\!\!\!\right\rangle\!\!\!-NO_2 \quad (1)$$
$$\text{(pNP)}$$

Immediately after a BIS-TRIS or TRIS† buffer solution of the metal complex was mixed with a solution of NPP at fixed ionic strength (typically 0.100 mol dm^{-3} NaCl), an increase of absorbance at 400 nm due to formation of 4-nitrophenol was observed. The behaviour of the analogous lanthanide(III) (2.2.2) complexes are strikingly different from that of the (2.2.1) complexes in that they irreversibly deligated to form precipitates immediately after mixing so rendering them inactive.‡

Changes of the absorbance§ were recorded in the presence of an excess of catalyst to satisfy pseudo-first-order rate conditions [eqns (2), (3)]. Plotting ln (A_∞ − A) vs. reaction

$$1 + NPP \underset{k_1}{\overset{k_1}{\rightleftharpoons}} [1\cdot NPP] \overset{k_2}{\longrightarrow} 1 + pNP + P_i \quad (2)$$

$$k_{p1} = k_2 [1]_0/(K_M + [1]_0), \quad K_M = (k_1 + k_2)/k_1 \quad (3)$$

time (t) resulted in linear slopes from which rate constants (k_{p1}) were obtained. The concentration of the metal complexes was varied to see if saturation of k_{p1} could be observed. As shown in Fig. 1, the rate constants were linear up to concentrations 8

mmol dm^{-3} 1a and 4 mmol dm^{-3} 1b, indicating that K_M is much larger than [1]$_0$ in this range. Precise measurements of rates at higher concentrations was hampered by complicating phenomena, e.g. formation of precipitates presumably due to association of the metal complexes.¶ A maximum rate constant (k_{p1}) of 1.7 × 10^{-4} s^{-1} (k_{bi} = k_2/K_M = 4.3 × 10^{-2} dm^3 mol^{-1} s^{-1}) was observed at pH 7.5 at 50 °C. Therefore, a *ca.* 10^4-fold enhancement of the hydrolysis rate is achieved in the presence of 4.0 mmol dm^{-3} 1b‖

It was found that the values of k_{p1} increased with increasing pH of the reaction medium (Fig. 2). Since the europium(III) complex 1b decomposes at pH > 8.5–9.0,** the pH range 7.0–8.5 was selected for study. Analysis of data from potentiometric titrations shows that the acidity constants (pK) of the lanthanum(III) and europium(III) complexes are, respectively, 9.1 and 7.8,[10]†† with the lower pK value of the europium(III) complex being typical.[11] From the calculated concentration of the lanthanide (2.2.1) hydroxides [HO–Ln(2.2.1)], the increase of rate constants over pH was fitted. As shown in Fig. 2, the broken lines from the simulated fit agreed well with the observed k_{p1} values indicating that the hydroxide was the active catalytic species.

As shown in the inset of Fig. 2, the europium(III) complexes truly catalyses the hydrolysis of NPP. The observed turnover number is 4 at pH 8.5 and 50 °C.‡‡ Reduced catalytic activity with time can be explained by the nature of a product of the hydrolysis. Thus the inorganic phosphate product not only competes with NPP, but also induces decomplexation of the lanthanide complexes.§§

$$\begin{matrix}\text{Ln}^{3+}\\ N\quad O\quad N\end{matrix} \quad 3\,Cl^-$$

1a Ln = La
1b Ln = Eu

Fig. 1 Effect of concentration of the metal complexes on the pseudo-first-order rate constants at pH of 8.0 (1a) and 7.5 (1b)

Fig. 2 pH dependence of the pseudo-first-order rate constants for the hydrolysis of NPP at 50 °C. The concentration of the lanthanide(III) (2.2.1) chlorides is 4.0×10^{-4} mol dm^{-3}. The broken lines are calculated based on the observed pK values and the initial concentration of the metal complexes assuming the hydroxide to be the active species. Inset: observed catalytic turnover numbers *vs. t* when the europium(III) complex is employed for the hydrolysis of NPP at pH 8.5 and 50 °C. The concentrations of the metal complex and NPP are 4.0×10^{-4} and 4.0×10^{-2} mol dm^{-3}, respectively.

In conclusion, both enhancement of the hydrolysis rate and truly catalytic turnover are achieved when lanthanide(III) (2.2.1) complexes are applied for the hydrolysis of NPP. Good correlation between the pH dependence of the rate constants and the concentration of the lanthanide (2.2.1) hydroxides suggests that this species behaves as a nucleophile.

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Footnotes

† BIS-TRIS and TRIS are commercial names of bis(2-hydroxyethyl)-iminotris(hydroxymethyl)methane and tris(hydroxymethyl)aminomethane respectively, and TRIS was employed except at pH 7.0, where BIS-TRIS was utilized. Concentrations of the BIS-TRIS and TRIS are fixed at 0.010 mol dm^{-3}. Mechanisms involving general base catalysis can be excluded because no noticeable change of the rates with the concentration of buffers was observed.

‡ The difference can be most clearly demonstrated when the concentration of NPP is adjusted to be same as that of metal complexes. This dramatic contrast confirms the earlier observation that lanthanide(III) (2.2.1) complexes have larger stability constants than the corresponding (2.2.2) and (2.1.1) complexes. See ref. 9 for stability constant values.

§ The molar absorptivity of 4-nitrophenol at 400 nm changes from 10 900 (pH 7.0) to 16 500 dm^3 mol^{-1} cm^{-1} (pH 8.5)

¶ The precipitates can be redissolved to give the intact lanthanide complexes by lowering the concentration. The reversibility differentiates the process from the aforementioned deligation.

‖ The rate constant of the uncatalyzed hydrolysis is 6.0×10^{-8} s^{-1} at 50 °C, pH 7.0 [See ref. 2(b)].

** The major pathway of decomposition is decomplexation resulting in formation of an insoluble precipitate. The IR spectrum of the precipitate is the same as that of samples prepared from metal chlorides under the same conditions.

†† Preliminary results from a time-resolved luminescence study show that the europium complex in aqueous solution forms an inner-sphere complex with three molecules of water at neutral pH.

‡‡ The lanthanum complex shows similar catalytic turnover at pH 9.0.

§§ Addition of excess sodium hydrogen phosphate and/or sodium dihydrogen phosphate to the reaction mixtures induces precipitation of lanthanide(III) phosphates *via* decomplexation. Analysis of the precipitate by FT-IR spectroscopy confirms the absence of the cryptate ligand.

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